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PREPARATION OF BRIDGED BICYCLOALKANES VIA INTRAMOLECULAR [2+2] CYCLOADDITIONS OF KETENES A SHORT TOTAL SYNTHESIS OF (±)-CLOVENE.

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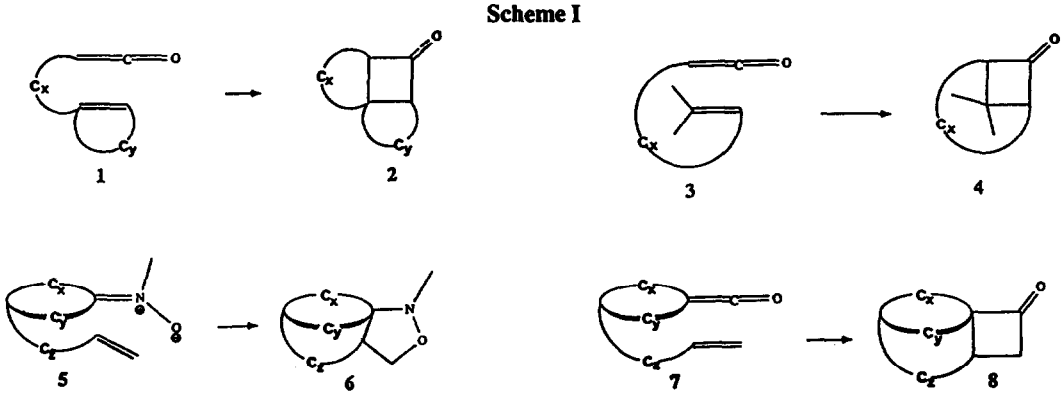
Summary: The preparation of a bridged bicyloalkane via an intramolecular ketene-olefin cycloaddition reaction in the context of a total synthesis of clovene is described.

The synthetic potential of the intramolecular ketene-olefin cycloaddition reaction is now widely appreciated.[2] This method has been primarily directed toward the construction of fused polycarbocycles, eg. **1** → **2** (Scheme I). However, when the olefin and ketene are separated by a 3 or 4 carbon tether and the terminal carbon of the olefin is disubstituted, bridged bicyclic adducts are favored via a regioisomeric head to tail type of cycloaddition, cf. **3** → **4**.[2b,c,g,m,n] As a result of our experience with the intramolecular cycloaddition reactions of exocyclic nitrones **5** to afford bridged bicycloalkanes of the general structure **6**,[3] we became interested in the analogous ketene

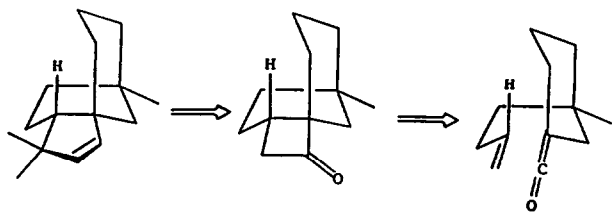
Scheme I



olefin cycloaddition (**7** → **8**) which would produce the head to head bridged tricarbocyclic adducts **8**. Herein, we document the feasibility of the cyclization process in the context of a total synthesis of (±)-clovene (**11**),[4] an acid-catalysed rearrangement product of caryophyllene.[5]

Our retrosynthetic analysis featuring the intramolecular cycloaddition reaction as the key step is shown in Scheme II. We anticipated that the cyclization of **9** would be stereocontrolled and produce only diastereomer **10** based on similar stereochemical preferences observed in **1** → **2** ketene-olefin cycloaddition reactions.[2] That is, stereoisomer **10** embodies a *cis*-fused bicyclo[4.2.0]octane substructure and is much less strained than the alternative diastereomer, the C(2) epimer,

Scheme II

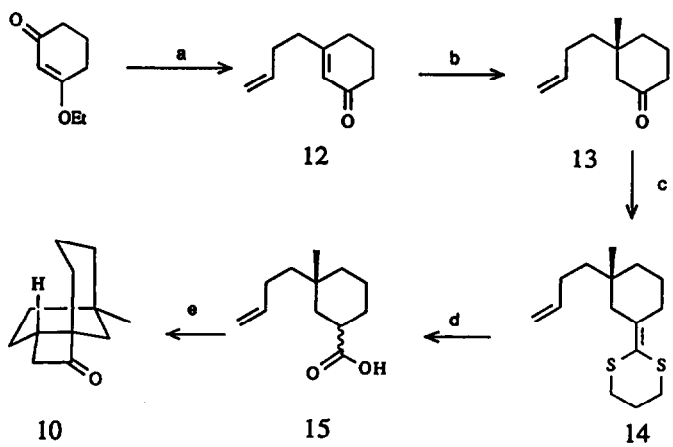


11 10 9

which possesses a *trans*-fused subunit.[6] The cycloadduct **10** is suitably functionalized for conversion to clovene, requiring only ring expansion of the cyclobutanone, geminal dimethylation and a carbonyl to olefin functional group transformation.

The synthesis of the cycloaddition substrate, carboxylic acid **15**, was straightforward and is outlined in Scheme III. Conjugate addition of lithium dimethyl cuprate to the readily available enone **12** afforded disubstituted cyclohexanone **13** (90%). Carbonyl homologation of cyclohexanone **13** to carboxylic acid **15** was accomplished according to the ketene dithioacetal protocol.[8] Thus, treatment of **13** with 2-lithio-2-trimethylsilyl-1,3-dithiane gave ketene dithioacetal **14** (70%). Hydrolysis of ketene acetal **14**

Scheme III



10 15 14

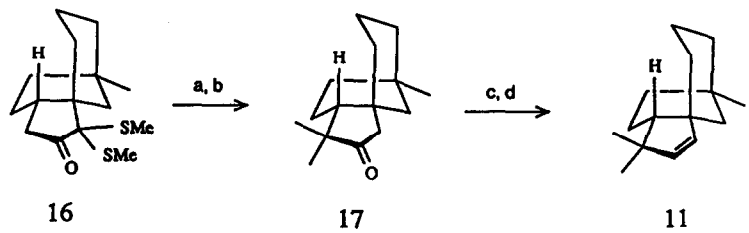
Reagents (a) $CH_2CHCH_2CH_2MgBr$; H_3O^+; (b) $LiMe_2Cu$, THF; (c) 2-lithio-2-trimethylsilyl-1,3-dithane; (d) $HgCl_2$, TFA, MeOH; NaOH, MeOH; (e) N-methyl-2-chloropyridinium iodide (4 equiv.), NEt_3 (8 equiv.), CH_3CN.

using the Chamberlin procedure ($HgCl_2$, TFA, MeOH; 88%)[9] afforded a diastereomeric mixture of methyl esters (55:45) which was then saponified to produce the desired carboxylic acids **15**.

The mixture of cyclohexane carboxylic acids **15** was subjected to our recently developed procedure for the direct conversion of enoic acids to the corresponding [2+2] cycloadducts.[10] Thus, syringe pump addition of **15** to NEt_3 (8 equiv.) and N-methyl-2-chloropyridinium iodide (4 equiv.) in refluxing acetonitrile (final concentration of **15** = 0.15M) gave a single cycloadduct **10** in yields ranging from 35-47% after column chromatography. In our hands, ketene generation and cyclization using the corresponding acid choride was inferior (7-10%).[2c]

The stereochemical assignment was quickly confirmed upon conversion of the tricyclic ketone **10** to clovene (**11**, Scheme IV). The crucial ring expansion of the cyclobutanone substructure of **10** was effected by employing a procedure reported by Knapp.[11] The anion derived from tris(methylthio)methane smoothly added to cyclobutanone **10** to provide an intermediate cyclobutanol which did not require treatment with Cu(I) or Hg(II) salts to effect rearrangement as described in the Knapp procedure. Instead, we observed that an NMR sample of the cyclobutanol adduct in $CDCl_3$ rearranged slowly, which led to the discovery that brief treatment with aqueous HCl in $CHCl_3$ promoted facile rearrangement to the cyclopentanone **16** (66% overall). Next, the gem-dimethyl group was installed

Scheme IV



16 **17** **11**

Reagents: (a) NaH, MeI, DME; (b) RaNi, acetone; (c) NH_2NHTs, MeOH; (d) BuLi, TMEDA; H_3O^+.

by permethylation of **16** (NaH, MeI, DME; 75%)[12] and desulfurization (deactivated RaNi, acetone, 79%) to provide the cyclopentanone **17**. Finally, transformation of the carbonyl functionality of ketone **17** to an olefin moiety (NH_2NHTs, MeOH; 4 equiv. BuLi, TMEDA; H_3O^+; 55%)[13] provided clovene which was identical in all respects with an authentic sample.[5c]

In conclusion, this relatively short total synthesis of clovene (nine steps from cyclohexanone **12**) further illustrates the utility of intramolecular [2+2] cycloaddition reactions of ketenes for the rapid assemblage of tricarbocyclic rings systems. Moreover, a variety of tricarbocyclic ring systems **8** can, in principle, be constructed by extension of this strategy and should also be of value in the synthesis of other natural products. These possibilities are currently being considered in our laboratories.

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